The Structure of Neuritic Plaques in the Cerebral Cortex of Aged Rats

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Abstract. Discrete patches of spongiform degeneration have been found in the cerebral cortices of three rats, 28 and 30 months of age. Many of these patches have in their midst a central nonvacuolated region containing a star-shaped homogeneous core. Using Congo red stain, there is evidence for the presence of amyloid in this core. In the electron microscope, this central region is seen to be composed of degenerating and abnormal neuronal processes, reactive neuroglia, and extracellular filamentous material with the fine structural characteristics of amyloid. Microglial cells are uniquely modified to accommodate bundles of these extracellular filaments, which are often contained in furrows that deeply invaginate the surfaces of these cells. On the basis of its three main constituents, the central region is considered to be a form of neuritic plaque. The large complex clearings in the vacuolar region of each lesion appear to be formed by the coalescence of smaller vacuoles in the surrounding neuropil.

Key Words: Amyloid, Neuritic plaques, Rats.

INTRODUCTION

Neuritic plaques are pathological entities which occur in the central nervous systems of man and certain other animals. Electron microscopically, neuritic plaques are characterized by the presence of three components; namely, degenerating neuronal processes, reactive neuroglial cells, and amyloid filaments, although the admixture of these components can vary, depending upon the factors which cause the plaques to be produced. One form of neuritic plaque is the senile plaque, which occurs in both normal and demented elderly people (1), as well as in individuals with Alzheimer's disease (2, 3). While such plaques contain all three components, they have the additional feature of the cytoplasm of axons and dendrites containing aggregates of helical filaments. However, these paired helical filaments seem to be species-specific, since they are absent from the neuritic (senile) plaques in aged dogs (4) and aged monkeys (5). It is generally believed that neuritic (senile) plaques are not normally formed within the brains of other aging mammals, including rats and mice (6, 7).

Another group of disease processes that can lead to the formation of neuritic plaques is the subacute spongiform virus encephalopathies such as Cruetzfeldt-Jakob disease, kuru, and scrapie (8). Although none of these dis-

eases occurs naturally in rats and mice, experimental transmission of certain scrapie agents to these rodents may induce their brains to form neuritic plaques (6, 9, 10, 11, 12).

This report describes degenerative lesions which have been encountered in the brains of three old rats taken from a standard aging colony. These lesions are discrete patches of spongiform degeneration and are of particular interest because electron microscopy shows them to contain the three major components of neuritic plaques; namely, degenerating neuronal processes, reactive neuroglial cells, and extracellular fibrillar material which has the features of amyloid. To our knowledge, this report presents the first account of neuritic plaques being formed in the brains of rats without experimental intervention.

MATERIALS AND METHODS

The cerebral cortices containing the lesions described in this report were taken from one 28-month-old and two 30-month-old male rats which came from a colony of outbred Sprague-Dawley rats maintained at Charles River Breeding Laboratories (Wilmington, MA). The rats in these aging colonies are retired breeders, set aside in group cages at 11 months of age. The rats receive food and water *ad libitum* and the colonies are maintained under barrier husbandry conditions, so that they are free from infectious diseases. The 50% survival time for these rats is approximately 26 months of age.

The rats were delivered to our laboratories in filtered cages and sacrificed within 18 hours of arrival. Fixation of the brain was by a two-stage vascular perfusion using aldehyde mixtures described by Reese and Karnovsky (13). An initial perfusion was carried out with a solution of 1% glutaraldehyde and 1% paraformaldehyde in 0.08 M cacodylate buffer with $CaCl_2$ at pH 7.2, and the fixation was completed with a solution containing 4% paraformaldehyde and 5% glutaraldehyde in the same buffer. Each animal was placed in a plastic bag and refrigerated overnight, so that fixation was complete before the brain was exposed and removed. For this study, blocks of somatosensory and auditory cortex corresponding to Krieg's areas 3 and 41, respectively (14), were removed for processing for electron microscopy. These blocks were post-fixed in 2% osmium in 0.1 M cacodylate buffer, dehydrated in a graded series of ethanols, and embedded in Araldite. In addition, some of the remaining tissue was embedded in paraffin and stained with Bodian silver method and with Congo red.

No other examples of the degenerative cerebral lesions were encountered in a survey of semithin toluidine blue-strain sections of cerebral cortex from 35 additional old rats, 28 to 30 months of age, among which were four rats taken from the same group as the three found to have the cerebral pathology to be described. Such pathology has also not been encountered in any of the more than 250 rats, 1 to 26 months of age, examined during the course of our studies of aging rat cortex.

RESULTS

Light Microscopy

The spongiform degeneration apparent in the cerebral cortices of the three rats showing the pathological changes to be described was not spread evenly throughout the cortical layers. Rather, it was usually confined to patches within layers III through V, and occurred with variable frequency, so that, in semithin sections taken from blocks of tissue 4-mm wide and containing the full thickness of cortex, there were from one to six well-defined regions of vacuolization.

Further, in each of the three animals, the degenerative changes were much more pronounced in the somatosensory cortex (area 3), than in the auditory cortex (area 41).

Semithin sections through the patches of vacuolar degeneration revealed that many of them had a central region in which there was a star-shaped core of homogeneous, basophilic material (Fig. 1). This core measured 15 to 30 nm in diameter, and profiles that appeared to be swollen, and only faintly stained, interdigitated with its radiating extensions. A similar appearance was also observed in paraffin sections stained by the Bodian technique, but in this case the star-shaped core was much more obvious, because of its intense argyrophilia, and because the thicker sections showed the surrounding vacuolar region to better advantage. Because it seemed likely that this core was composed of amyloid, some paraffin sections were stained with Congo red. When such sections were examined with polarized light, the cores appeared green and displayed an almost crystalline birefringence (Fig. 2).

It should be pointed out that not all the patches of vacuolar degeneration contained such cores. In some cases, this apparent absence was because the section did not pass through the center of the patch. In other examples, especially of smaller patches, serial semithin section analysis did in fact show a core to be absent. However, further analysis of one such small patch of vacuolar degeneration revealed the presence of loosely arranged filaments passing among degenerating neuronal processes, reactive neuroglia, and large complex vacuoles.
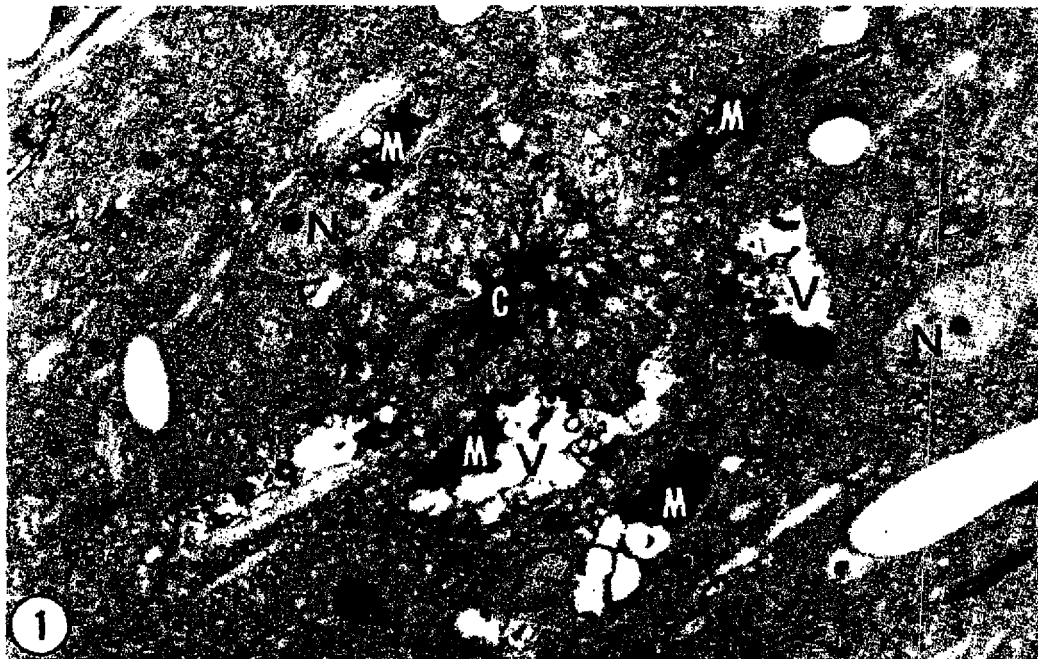

Fig. 1. Small lesion in somatosensory cortex of an old rat. A neuritic plaque with a star-shaped core (C) occupies the central region. Microglial cells (M) are frequently associated with the large complex vacuoles (V) occupying the neuropil surrounding the plaque. Neurons (N) exhibit no vacuolar changes. ×1,200.

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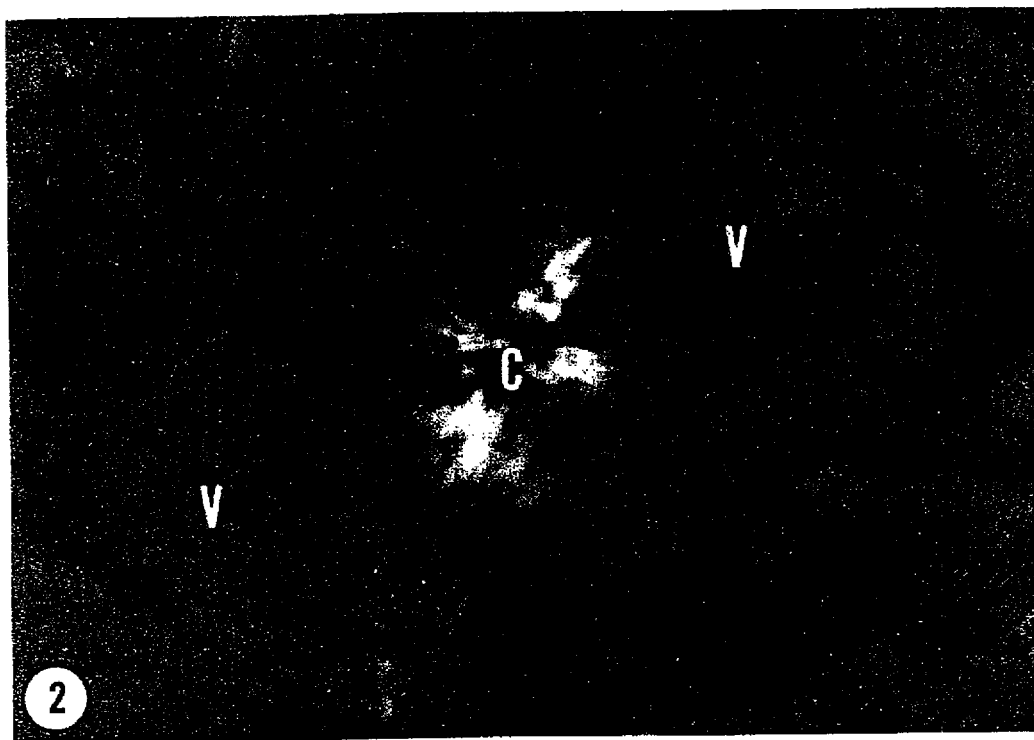omplex

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Fig. 2. Neuritic plaque stained with Congo red and photographed with polarizing optics. In the light microscope, this birefringent stellate core (C) appears green against the dark background. Vacuoles (V) occupy the surrounding neuropil. ×1,800.

The large complex vacuoles associated with the lesions were located in the neuropil, and they were not observed to occur within the cell bodies of neurons, even though neurons were sometimes completely surrounded by vacuolated neuropil. Indeed, the neuronal cell bodies, both within and around the areas of degeneration, appeared quite normal for the ages of the rats examined, and their increased lipofuscin content and somewhat folded nuclei were quite characteristic for rats older than 27 months of age (15).

Although no changes in the frequency or morphology of neuronal cell bodies were apparent in the immediate vicinity of the lesions, there were obvious changes in the neuroglial cell population. Thus, there was always an increase in the densely stained microglial cells. This increase correlated with the amount of vacuolization, and the cell bodies of the microglia frequently bordered directly upon the complex vacuoles (Fig. 1). In contrast to the microglia, there was no apparent increase in the number of asytrocytes in the vicinity of the lesions, although hypertrophied astrocytic processes were frequently visible in the semithin sections.

Electron Microscopy

When this material was examined with the electron microscope, it was possible to distinguish between the central plaque region (Figs. 3−7) and the vacuolated region (Figs. 8 and 9) of the lesions, although there was a gradual transition between these two regions.

Fig. 3. Central region of the lesion, in which bundles of extracellular filaments (arrows) occur among astrocytic (A), microglial (M), and oligodendroglial (O) processes. Degenerating neuronal processes (asterisks) are also present. This constellation of degenerative changes constitutes a neuritic plaque. ×8,000.

Fig. 4. At higher magnification, the transversely sectioned individual filaments appear as electron-dense circles with lucent cores (arrows). When sectioned longitudinally or obliquely (arrowheads), they are seen as parallel dark lines separated by lucent lines. ×83,000.

Central region: This region of each lesion was characterized by the presence of numerous bundles of extracellular filaments which were woven among the neuronal and neuroglial processes (Fig. 3). The packing density of these filaments was, however, not so great as that demonstrated in neuritic plaques of humans (16). When they were sectioned transversely, the individual filaments within the bundles were seen to be about 10 nm in diameter and to have the appearance of electron-dense circles with lucent cores. Thus, the filaments seemed to be hollow (Fig. 4). This appearance was consistent with the characteristic ultrastructural appearance of amyloid protein: pentagonal plates as-

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Fig. 5. Bundles of filaments in the extracellular space frequently indent the surfaces of astrocytes (A) and microglia (M). As typical for animals of such advanced age, the microglia contain clumps of electro-dense debris (arrows). In the absence of neuronal and neuroglial processes, the filaments weave among each other (asterisk). ×25,500.
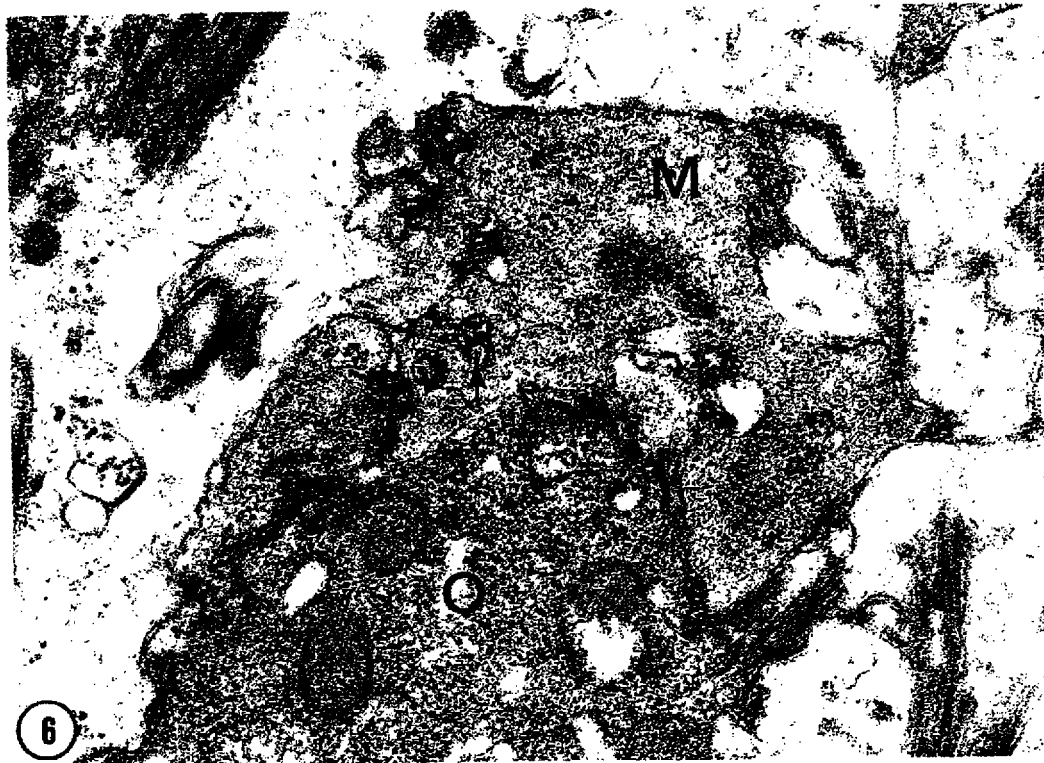
Fig. 6. Microglial (M) and oligodendroglial (O) processes surrounded by astrocytic processes. Of the three neuroglial cell types, the microglia are most modified to accommodate the bundles of filaments. Arrows indicate two bundles of filaments contained within deeply invaginated portions of the microglial cell plasma membrane. ×37,500.

sembled as columns of stacked discs (17, 18). Within the bundles, the hollow filaments lay side by side in contact with their neighbors, assembled into single or double rows (Fig. 4). Because the filaments appeared hollow, in sections passing parallel to the lengths of the bundles, individual filaments displayed two parallel dark lines, representing their dark walls, separated by a more lucent interval. Not infrequently, bundles of filaments in contact produced images of several parallel dark lines separated by more lucent intervals. In the core of the plaque, cellular processes were less frequent, and there were patches in which closely-knit bundles of filaments were woven randomly among each other (Fig. 5). It is believed that these filaments correspond to the amyloid demonstrated with the Congo red staining technique.

Astrocytic processes were a prominent feature of the central region. The individual processes were generally more voluminous (Figs. 3–7) than those observed in normal cortical material (19, 20), and their surfaces were indented by gutters in which the bundles of filaments are accommodated (Figs. 5 and 7). For the most part, the cytoplasm of the astrocytic processes was quite lucent and was filled by a flocculent matrix in which there were few astrocytic filaments, mitochondira, microtubules, and free ribosomes. Occasionally, however, astrocytic processes containing large bundles of cytoplasmic filaments were encountered (Fig. 3).
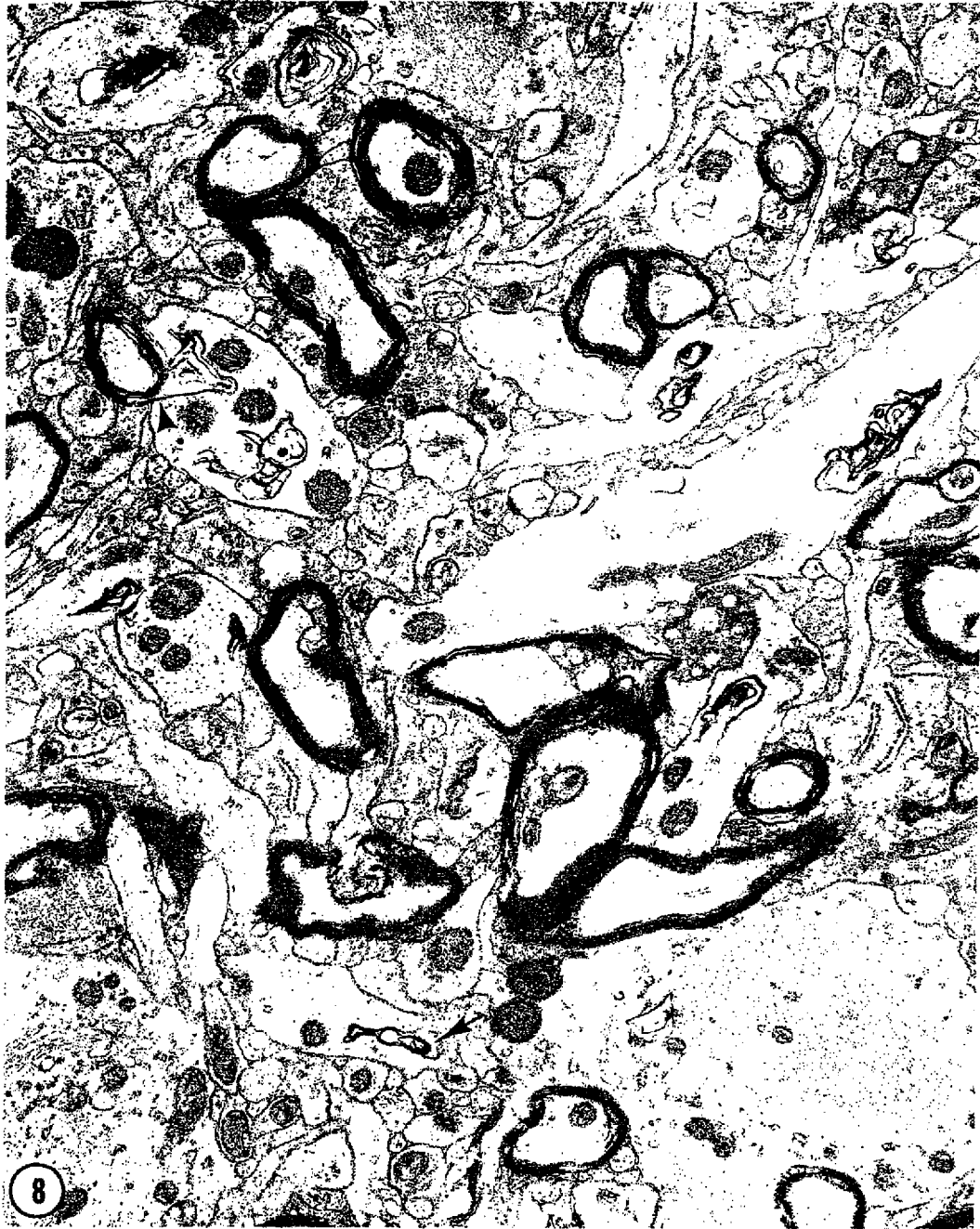
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Fig. 7. Central region of the lesion where bundles of filaments appear to stream from both oligodendroglia (O) and microglia (M). Abnormal neuronal processes display a variety of degenerative changes. ×20,000.

Fig. 8. In the vacuolar region of a lesion, abnormal neuronal processes are dispersed among apparently normal elements. The small membranous inclusions which occur in many dendritic profiles are derived from mitochondria, invaginated dendritic membranes (arrow), or neighboring myelinated axons (arrowhead). ×14,000.

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Fig. 9. The edge of a large vacuole shows evidence of continuing expansion into the surrounding neuropil by means of the coalescence of other vacuoles, which are indicated with asterisks. ×30,000.

The microglial cell processes in this central region of the lesion were dispersed throughout the neuropil. As is typical, the microglial processes had the appearance of angular profiles with relatively dense cytoplasm, and the larger ones contained long cisternae of rough endoplasmic reticulum, in addition to mitochondria, free ribosomes, and small membrane-bound, electron-dense inclusions (Fig. 5). As appropriate for animals of such advanced age, clumps of dense debris and large membrane-bound vacuoles frequently appeared within both the cytoplasm of the larger microglial processes an the perinuclear cytoplasm (20). Extracellular bundles of amyloid filaments were often enclosed within furrows formed by infoldings of the plasma membranes of the microglial processes. Some of these furrows were quite deep (Fig. 6), and much more complex than the rather simple gutters in which the astrocytic processes accommodated the filaments. Frequently, examination of microglial processes, associated with bundles of the filaments, gave the impression that the filaments were intracellular. However, through an analysis of serial thin sections, it became apparent that, in the majority of cases, the filaments were contained within furrows and indentations of the microglial cell surface, and that the intracellular appearance was due to the surrounding plasma membrane being obliquely sectioned so that it did not produce a clear image.

Bundles of extracellular filaments often seemed to pass into the cell bodies and processes of oligodendroglia (Fig. 7), as well as microglia (Fig. 5) and astrocytes. However, once again this apparent "streaming" of filaments from the cytoplasm of all three types of neurolgial cells was probably an illusion caused by an inability to see the image of the unusually irregular plasma membranes which separate the filaments from the neuroglial cell cytoplasm. This relationship between the filaments and the neuroglial cells was inconsistent with observations of amyloid in human tissue, where filaments have been demonstrated without any surrounding membrane inside cells (5, 21).

The axons and dendrites in this region displayed a variety of morphological alterations. A consistent feature of many of the dendritic profiles was small irregular membranous inclusions which were often contained within the cytoplasm (Figs. 7 and 8). In this material, the derivation of these inclusions seemed to be from three different sources. One source was the dendritic membrane itself, for reconstructions from serial thin sections revealed that many of the inclusions were connected to the plasma membrane, so that they seemed to be produced by whorls of excess plasma membrane invaginating into the dendrites (Fig. 7). Sometimes a thin sheet of astrocyte accompanied the internalized dendritic membrane. A second source of the small whorls was individual mitochondria from which portions of the inner and outer membranes evaginate to form irregular blebs. The third observed source was adjacent myelinated axons, segments of which appeared to be drawn into the dendritic cytoplasm. Sometimes only the outer two or three lamellae of the myelin sheath were involved, while in other examples both the myelin sheath and the underlying axolemma were evaginated into neighboring dendrites (Figs. 7 and 8). Membranous whorls with an appearance similar to those found in the sites of degeneration have also been encountered in the dendrites of cortical neuropil from old rats showing no signs of vacuolar degeneration (22), and they have also

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been encountered in areas of rat cortex containing degenerating axon terminals induced by experimental lesions being placed within either the thalamus or the corpus callosum (unpublished results).

Dendritic spines were rarely observed within this central region of the vacuolated lesions, although in normal material these spines account for about 5% of the volume of the neuropil. The lack of spines was perhaps accentuated by the low incidence of typical axon terminals, whose profiles normally make up some 20% of the normal cortical neuropil of aging rats (unpublished data).

The axon terminals that were present in this central region displayed a range of pathological alterations. A few terminals, some with visible synaptic junctions, appeared to be degenerating, as evidenced by their increased electron density and an enveloping astrocytic process. Other profiles, also with frequent visible synaptic junctions and/or synaptic vesicles, contained dense membrane-bound inclusions, some of which appeared to be derived from mitochondria (Fig. 7). Yet, other axon terminals were filled with vesicles which had contents of varying electron density and were larger and less regular in shape than normal synaptic vesicles (Fig. 7).

The myelinated axons were also subject to morphological alterations. Most of them were affected by the type of disturbance described above, in which the myelin lamellae spread apart, increased in length, and were apparently drawn into dendrites. Although this form of axonal alteration most frequently involved evagination into dendrites, the separated lamellae of myelin also evaginated into neighboring astrocytic processes, or invaginated into the cytoplasm of the axon (Fig. 8). Despite these changes in some of the myelin sheaths, the majority of axons had a normal axoplasm. A few showed either an electron-dense axoplasm, which indicated that they were undergoing degeneration, or accumulations of dense membrane-bound bodies.

Vacuolar region: Proceeding outward into the region of complex vacuoles, there was a gradual change in the form of the neuropil, which began to contain large empty regions and an increasing proportion of neuronal process which appeared to be normal in comparison to those in the central region. This was particularly true of axon terminals, myelinated axons, and dendritic spines (Figs. 8 and 9). Extracellular amyloid filaments were still present, although the individual bundles were generally smaller than in the central region and were restricted to small areas, rather than being dispersed throughout the neuropil. Irregular membranous inclusions still appeared within dendrites, and the sheaths of many myelinated axons still exhibited focal disturbances.

The largest of the vacuoles, those seen so strikingly in the light microscope, were generally incompletely bound by membranes and looked like localized clearings in the neuropil, with the free ends of some of the disrupted membranes extending into and included within the vacuolar lumen (Fig. 9). There was no evidence of lysosomal digestion associated with the vacuoles, and the fate of the evacuated material was not evident, but small pockets of irregular clear spaces extending into the neuropil at the edges of some of the vacuoles suggested that they were still expanding through a coalescence of smaller vacuoles (Fig. 9).

The exact location of the initial vacuolization of the neuropil was not appar-

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ent, although disturbances within neuronal processes may initiate this degenerative change, and subsequent coalescence of increasingly larger vacuoles may produce the effect observed. It is clear, however, that the perikarya of neurons were not involved, as is characteristic for many of the subacute spongiform encephalopathies (8, 12, 23).

Outlying neuropil: The appearance of the neuropil in the area peripheral to the vacuoles was generally unremarkable. Profiles of degenerating neuronal processes were encountered, but their number was not much greater than would be encountered throughout the neuropil within the cerebral cortex of other animals of this advanced age. The vascular system also showed no unusual features and the neuronal cell bodies, as stated above, were typical of animals of this age.

DISCUSSION

This report demonstrates that degenerative changes can occur spontaneously within the cerebral cortex of some rats, leading to the formation of a constellation of changes that together constitute neuritic plaques. The extracellular filaments within these plaques in the rat brain have the fine structural characteristics of amyloid (2, 17, 18), although not the packing density and configuration of neuritic plaque amyloid described in the literature (4, 5, 6, 11, 12, 16). After staining with Congo red, the cores formed from the filaments showed the histochemical characteristics of amyloid. To our knowledge, no other extracellular fibrillar material has been described in the neuropil of the rat brain, and thus it is concluded that the extracellular filaments must be a form of amyloid.

This report contributes to an understanding of the etiology of amyloid deposits in the brain. In the present material, there is no apparent vascular amyloidosis, and no blood vessels are found within the central region of the plaques, so that what seems to be an early stage of amyloid deposition appears to be quite independent of any changes in the vascular system. In searching for a cause or primary mechanism of the disturbance, the answer should probably be sought in the outer zones of the lesion. This is because the appearance of the plaques suggests that the center represents a "scar," which has resulted from the filling of vacuolated regions of neuropil, and the pathological change seems to be spreading outward, creating zones of graded pathology. Thus, the vacuolated region with the increased numbers of microglial cells represents the region of active change. The most striking alteration within this region is the membrane disturbances. A wide range of membranes is affected, including those of mitochondria, the sheaths of myelinated axons, and all plasma membranes involved in the large focal clearing in the neuropil. There is no evidence that the extracellular filaments of amyloid are the toxic agent, for the filaments are not always present at the sites of neuropil degeneration and vacuolization.

Although this study has not completely explained the role of the microglial cells in the synthesis or processing of amyloid, it is apparent that the amyloid filaments are not being released from the cells through exocytosis, nor does it appear that the filaments are being synthesized within the rough endoplasmic reticulum for extracellular release. It is possible that the microglial cells are

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producing amyloid precursors following lysosomal digestion of a phagocytosed material of unknown origin and these amyloid protein molecules assemble extracellularly into fibrillar form through a physicochemical mechanism.

Most examples of neuritic plaques which have been described in the brains of humans and animals fall into two categories: (1) amyloid plaques associated with a variety of subacute spongiform encephalopathies such as kuru, Creutzfeldt-Jakob disease, and scrapie (8) and (2) senile (neuritic) plaques, including the plaques of Alzheimer's disease and Down's syndrome (16). The basic similarities between these rat plaques and the plaques described in the literature are that they are localized foci consisting of degenerating neuronal processes, reactive neuroglial cells, and extracellular amyloid filaments.

The spongiform nature of the more advanced vacuolar changes present in these three rat brains is similar to that found in some of the subacute spongiform encephalopathies (8, 12, 24), but none of these transmittable diseases has been reported to occur naturally in rats. Scrapie has been experimentally transmitted to rats, but the transmission occurs only after intracerebral inoculation of infected material (17). Furthermore, in the present rat material, there is none of the vacuolization of the neuronal cell bodies that occurs in scrapie-infected sheep, rats, and mice (12) and in kuru-infected monkeys (23). Indeed, in these rats, the neuronal perikarya seem to be remarkably resistant to vacuolar change.

The spongiform degeneration observed in these rat brains is not usually associated with senile plaque pathology, although recent reports suggest vacuolar changes can occur in association with Alzheimer's disease (25, 26). Also, although unique paired helical filaments appear within the degenerating neuronal processes of human senile plaques (27), they are not present in these rat plaques, but they are also absent from the senile plaques found in old dogs and monkeys (4, 5).

It may be concluded, therefore, that although similarities exist, there are also significant differences between pathological changes observed in these old rats and those occurring in the known pathological processes with which neuritic plaques have been associated. It is quite clear, however, that plaques represent one way in which a brain can respond to a damaging agent or process, and this report presents the first evidence that the rat brain can respond by producing plaques in the absence of experimental manipulation. The etiology of the plaques described here is not known. The three rats in which they occurred were old, but it is important to note that they were from the same group of animals and could have acquired the same infection.

ACKNOWLEDGMENTS

REFERENCES

1. Tomlinson BE, Blessed G, Roth M. Observations of the brains of non-demented old people. J Neurol Sci 1968;7:331-56

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2. Terry RD, Gonatas NK, Weiss M. Ultrastructural studies in Alzheimer's presenile dementia. Am J.Pathol 1964;44:269-97
3. Kidd M. Alzheimer's disease—an electron microscopical study. Brain 1964;87:307-21
4. Wisniewski H, Johnson AB, Raine CS, Kay WJ, Terry RD. Senile plaques and cerebral amyloidosis in aged dogs: A histochemical and ultrastructural study. Lab Invest 1970;23:287-96
5. Wisniewski HM, Ghetti B, Terry RD. Neuritic (senile) plaques and filamentous changes in aged rhesus monkeys. J Neuropathol Exp Neurol 1973;32:566-84
6. Wisniewski H, Bruce ME, Fraser H. Infectious etiology of neuritic (senile) plaques in mice. Science 1975;190:1108-10
7. Dayan AD. Comparative neuropathology of aging. Brain 1971;94:31-42
8. Lampert PW, Gajdusek DC, Gibbs CJ. Subacute spongiform virus encephalopathies. Am J Pathol 1972;68:626-52
9. Bruce ME, Fraser H. Amyloid plaques in the brains of mice infected with scrapie: Morphological variation and staining properties. Neuropathol Appl Neurobiol 1975;1:189-202
10. Chandler RL, Fisher J. Experimental transmission of scrapie to rats. Lancet 1963;2:1165
11. Field EJ, Raine CS, Joyce G. An electron microscopic study of scrapie in the rat. 1. The occurrence of amyloid bodies and deposits. Acta Neuropathol (Berl) 1967;8:47-56
12. Fraser H. The pathology of natural and experimental scrapie. In: Kimberlin RH, ed. Slow virus diseases of animals and man. New York: Elsevier, 1976:267-305
13. Reese TS, Karnovsky MS. Fine structural localization of blood-brain barrier to exogenous peroxidase. J Cell Biol 1967;34:207-18
14. Kreig HJS. Connections of the cerebral cortex. 1. Albino rat. A topography of the cortical areas. J Comp Neurol 1946;84:221-76
15. Vaughan DW, Vincent JM. Ultrastructure of neurons in the auditory cortex of aging rats, A morphometric study. J Neurocytol 1979;8:215-28
16. Wisniewski HM, Terry RD, Reexamination of the pathogenesis of the senile plaque. In: Zimmerman HM, ed. Progress in neuropathology. New York: Grune and Stratton, 1973;2:1-26
17. Bladen HA, Nylen MU, Glenner GG. The ultrastructure of human amyloid as revealed by the negative staining technique. J Ultrastruct Res 1966;14:449-59
18. Pinteric L, Painter RH. Electron microscopy of serum amyloid protein in the presence of calcium; alternative forms of assembly of pentagonal molecules in two-dimensional lattices. Can J Biochem 1979;57:727-36
19. Peters A, Palay SL, Webster DeFH. The fine structure of the nervous system. The neurons and supporting cells. Philadelphia: W. B. Saunders, 1976:233-48
20. Vaughan DW, Peters A. Neuroglial cells in the cerebral cortex of rats from young adulthood to old age: An electron microscope study. J Neurocytol 1974;3:405-29
21. Glenner GG, Page DL. Amyloid, amyloidosis, and amyloidogenesis. Int Rev Exp Pathol 1976;15:1-92
22. Feldman ML. Dendritic changes in aging rat brain. In: Nandy K, Sherwin I, eds. Aging brain and senile dementia. New York: Plenum Press, 1977:23-37
23. Lampert PW, Earle KM, Gibbs CJ Jr, Gajdusek DC. Experimental kuru encephalopathy in chimpanzees and spider monkeys. Electron microscope studies. J Neuropathol Exp Neurol 1969;28:353-70
24. Manuelidis EE, Gorgacz EJ, Manuelidis L. Interspecies transmission of Creutzfeldt-Jakob disease to Syrian hamsters with reference to clinical syndromes and strains of agent. Proc Natl Acad Sci USA 1978;75:3432-6
25. Flament-Durand J, Couck AM. Spongiform alterations in brain biopsies of presenile dementia. Acta Neuropathol (Berl) 1979;46:159-62
26. Rewcastle NB, Gibbs CJ, Gajdusek DC. Transmission of familial Alzheimer's disease to primates. J Neuropathol Exp Neurol 1978;37:679
27. Wisniewski HM, Narang HK, Terry RD. Neurofibrillary tangles of paired helical filaments. J Neurol Sci 1976;27:173-81